EXHIBIT 10

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

- - -

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	:	MDL NO. 2606

- - -

May 6, 2016

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P R O T E C T E D I N F O R M A T I O N

Videotaped deposition of ALLEN FELDMAN, M.D., taken pursuant to notice, was held at the law offices of Drinker Biddle & Reath, 1177 Avenue of the Americas, New York, New York, beginning at 9:06 a.m., on the above date, before Michelle L. Gray, a Registered Professional Reporter, Certified Shorthand Reporter and Notary Public.

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Q. This diagnosis of celiac occurred after this patient had exhibited celiac-like symptoms two years after starting to take the drug?
A. That you said resolved?
Q. That resolved after they stopped taking the drug. So we have a dechallenge here as well, right?
A. Exactly my point.
Q. So isn't that -- well, rephrase.
The diagnosis actually occurred on the day that she said she was vomiting and couldn't keep food down two different times. She was actually diagnosed with celiac, while vomiting, while on Benicar, right?
A. Right.
Q. The better practice for this would have been to code for celiac, right? The patient was diagnosed with celiac while throwing up on Benicar.
MR. PARKER: Objection.
THE WITNESS: But I'm

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confused, because it's saying that it resolved, but she's got celiac disease.
BY MR. SLATER:
Q. It resolved -- rephrase.
She was diagnosed with celiac. That doesn't mean she has celiac, right?
A. It doesn't?
Q. Okay. And --
A. I thought it does.
Q. And you think that anybody --
A. It means diagnosed, has celiac disease.
Q. Are you aware of the fact that there are many patients who were misdiagnosed with celiac when in fact they had spruelike enteropathy while taking Benicar and the other olmesartan drugs?
MR. PARKER: Objection.
BY MR. SLATER:
Q. Are you aware of that?

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A. What are you referring to?
Q. I'm referring to patients who were taking olmesartan. Do you know that some of those patients were diagnosed with celiac and that was a misdiagnosis. It was actually spruelike enteropathy that was causing those symptoms?
MR. PARKER: Objection.
THE WITNESS: Are you talking about the Mayo Clinic paper? Is that what you're referring to?
BY MR. SLATER:
Q. I'm talking about -- you can include that or any other information that you have. Do you know that that's something that was happening to patients?
MR. PARKER: Objection.
THE WITNESS: I know that they came to the Mayo Clinic with -- some of them came with the diagnosis of celiac disease.
BY MR. SLATER:

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Q. Which turned out to be wrong, right?
A. That did not respond to a gluten-free diet.
Q. In fact, they were negative for celiac serologies. They didn't respond to gluten-free diets. And it turned out that it was the Benicar causing their condition based on the dechallenges, right?
MR. PARKER: Objection.
THE WITNESS: Well, again, the way you're describing is not exactly how it's described in the paper. It's associated with. You're saying caused it.
BY MR. SLATER:
Q. The likelihood is if you have a series of 22 patients who are exhibiting similar constellations of symptoms consistent with a picture of celiac, but they're negative for celiac, they don't respond to a gluten-free diet, and their symptoms go away when they stop

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taking the olmesartan, the likelihood is the olmesartan is causing the condition, right?

MR. PARKER: Objection.

THE WITNESS: I think it's a possibility. But as -- in the paper, again, they're saying that there isn't the critical information needed to establish causality.

But according -- could we go back to this?

BY MR. SLATER:

Q. No. Let's stick where we are. I'm not talking about the paper. I'm talking about you, the head of the department.

The answer to my question is yes, when you have that picture, the likelihood is that the olmesartan is causing the symptoms, right?

MR. PARKER: Objection. Asked and answered.

THE WITNESS: You need to --

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I need to hear this question again.

BY MR. SLATER:

Q. The Rubio-Tapia patients, the likelihood is that the olmesartan was causing their constellation of symptoms, correct?

MR. PARKER: Objection.

THE WITNESS: The likelihood is -- so are you saying that is the cause?

BY MR. SLATER:

Q. That is the likely cause, right?

MR. PARKER: Objection.

THE WITNESS: Well, again, they didn't establish causality there.

BY MR. SLATER:

Q. I'm asking you. The likelihood is that the olmesartan was causing those patients' symptoms, correct?

A. I don't know. I think that

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there's a -- there is an -- there appears to be an association. I don't know if that's -- if olmesartan caused the symptoms.

Q. You'll agree with me that the patients in Rubio-Tapia demonstrated an association between their symptoms and olmesartan. We can agree on that?

A. Yes.

Q. The most likely explanation for their symptoms based on their history of their symptoms starting after they started taking olmesartan, not responding to a gluten-free diet, being negative for celiac serologies, and then having positive dechallenges where their symptoms went away when stopped taking the drug, that clinical picture, the likelihood is that the olmesartan was causing the symptoms, correct?

MR. PARKER: Objection.

THE WITNESS: I would say that was the only explanation that was posited.

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BY MR. SLATER:

Q. It's the only explanation you can posit right now, right?

A. Yes, based on what I know about what they presented.

Q. Okay. Now, let's go back to this adverse event report. I'll just make a note. It's not an interesting note. It has to do with what I'm supposed to do later.

We're going to come back to this one. We'll save it for when we get to -- not a big surprise -- when we get to talk about the request for celiac cases. We'll put these to the side, try to be more efficient on our time.

MR. SLATER: How are we doing on time? It's noon.

MR. PARKER: We're okay.

MR. SLATER: All right. Keep going? Great.

BY MR. SLATER:

Q. I'm going to now hand you Exhibit 127. Exhibit 127 is a MedWatch

EXHIBIT 11

AP&T Alimentary Pharmacology and Therapeutics

Olmesartan-associated enteropathy: results of a national survey

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SUMMARY

Background
Recently, a new enteropathy has been described: olmesartan-associated enteropathy. However, the association has been questioned: a phase 3 trial and a cohort study found no association between gastrointestinal events and olmesartan.

Aim
We collected French cases of sartan-associated enteropathy to describe further this entity, confirm or refute causality, and determine if the association exists with other sartans.

Methods
French gastroenterologists were invited to report cases of sartan-associated enteropathy and collect clinical, biological and histological data. Patients with diarrhoea and histological duodenal abnormalities were included.

Results
Thirty-six patients with olmesartan-associated enteropathy were reported, including 32 with villous atrophy and four without. There was only one patient with irbesartan-associated enteropathy. None of the patients died. Patients with villous atrophy had diarrhoea, vomiting, renal failure, hypokalaemia, body weight loss and hypoalbuminaemia. Thirty-one patients were hospitalised; four required intensive care. Anti-transglutaminase and anti-enterocyte antibodies were negative; anti-nuclear antibodies were positive (9/11). Endoscopic duodenal biopsies showed villous atrophy (32/32) and polyclonal intra-epithelial CD3+CD8+ lymphocytosis (11/11). Exactly, 14/15 patients responded to steroids and/or immunosuppressants, prescribed because of suspected autoimmune enteropathy. Ten olmesartan interruptions were followed by reintroductions before steroids or immunosuppressants. Interruptions were followed by remissions (9/10), but reintroductions were followed by relapses (9/9). Twenty-nine patients were in remission since olmesartan interruption, including 26 without immunosuppressants. Patients with normal villi had similar clinical characteristics, but mild histological abnormalities (intra-epithelial lymphocytosis and lamina propria lymphocytic infiltration).

Conclusions
Olmesartan causes a severe and immune-mediated enteropathy, with or without villous atrophy. Enteropathy associated with other sartans seems to be very rare.

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INTRODUCTION

Noncoeliac sprue encompasses several diseases[1]: tropical sprue,[2] refractory sprue,[3–9] low-grade T-cell lymphoma [10–12] and adult autoimmune enteropathy.[13, 14] More recently, Rubio-Tapia *et al.* have described 22 patients with severe, noncoeliac enteropathy who improved after discontinuation of olmesartan.[15] It has also been suggested that Olmesartan may account for a significant proportion of noncoeliac enteropathy, as reported in a series of 72 adult patients with villous atrophy and negative coeliac disease serology.[16] Sixteen of them were found to be treated with olmesartan, 15 of whom improved after olmesartan withdrawal. Several other cases have been reported.[17]

Olmesartan medoxomil, the prodrug of olmesartan, is an angiotensin II receptor blocker (ARB). It was approved in 2002 in the USA, and in 2003 in the European Union, for the treatment of hypertension. In the ROADMAP trial, a phase 3 trial performed in 4447 patients with diabetes mellitus, the rates of diarrhoea and abdominal discomfort were similar in the olmesartan and the placebo arm.[18, 19] More recently, a retrospective cohort analysis performed in 45 185 (116 721 patient-years) diabetic patients, compared olmesartan with other sartans and found no significant association between olmesartan and gastrointestinal disease-related hospitalisation.[20] Therefore, the association between enteropathy and olmesartan has been called into question.

Following the report by Rubio Tapia *et al.*,[15] we decided to perform a survey of enteropathy associated with olmesartan and other sartans in France. The aims of the present study were to describe further this new entity, to confirm or refute the causality of the association (by the study of olmesartan interruptions and reintroductions) and to determine if the enteropathy is associated with olmesartan only or with sartans in general.

PATIENTS AND METHODS

In July 2013, we sent an electronic alert to French gastroenterologists to inform them of the data reported by Rubio-Tapia *et al.* and invited them to report the cases of diarrhoea (either severe or not) associated with the use of sartans. We sent an email to Gastroenterologists working in University hospitals. In addition, a letter was sent to all Gastroenterologists, either in public hospitals or in private practice, using the electronic letter called Gastroscoop. This letter is published by the French National Society of Gastroenterology and sent to 2400 Gastroenterologists in France. We also contacted by email several Gastroenterology departments in French-speaking Belgium. Investigators were asked to report their observations to the pharmacovigilance unit to which their centre was affiliated and to participate in the cohort by filling out an anonymous, pre-specified electronic form. Clinical, biological and histological data were collected. Quantitative variables were expressed as median [range]. We included patients who had diarrhoea and abnormal histology on duodenal biopsies. We put the patients into two groups: patients with villous atrophy and those with normal villi and histological abnormalities such as intra-epithelial lymphocytosis or infiltration of lamina propria. The study was submitted to the ethical committee of Paris-Ile de France VII. This committee stated that there was no ethical issue related to this study.

RESULTS

Twenty-seven hospitals or medical centres reported 48 cases, including 47 with olmesartan and one with irbesartan. Data were available for 40 patients (completed electronic form), including 39 who received olmesartan and one who received irbesartan. One patient had normal duodenal biopsies and two patients did not have duodenal biopsies; these three patients were excluded from analysis.

Among the remaining 36 patients treated by olmesartan, 32 had villous atrophy and four had normal villi, but histological duodenal abnormalities.

Enteropathy with villous atrophy associated with olmesartan

Thirty-two cases (17 women) were reported. The patients were recruited in university hospitals ($n = 23$), general hospitals ($n = 7$) or private medical centres ($n = 2$). The median age was 70 years [46–91]. Seven patients had a past history of autoimmune or inflammatory disease (Table S1) and three patients had first-degree family history of autoimmune or inflammatory disease (two with coeliac disease, one with ulcerative colitis and one with rheumatoid arthritis). All patients received olmesartan for hypertension. Patients received six different formulations of olmesartan, including two in which olmesartan was combined with diuretics. The median dosage of olmesartan was 40 mg/day [10–60]. Sixteen patients received drugs other than olmesartan before the first symptoms of enteropathy. Concomitant medications differed between patients (Table S2). Therefore, there were no specific associations between olmesartan, other drugs

and enteropathy. Time between olmesartan prescription and first symptoms was 28 months [2–139].

Clinical, biological and histological manifestations

All 32 patients (100%) had diarrhoea, with a median number of 8 liquid stools per day [2–20]. Twenty-four patients (75%) had abdominal pain, which was rarely severe (n = 3). Eighteen patients (56%) had vomiting. Body weight loss was 18% [0–48]. Nine patients (28%) had extra-intestinal manifestations, which are described in Table S3. Twenty-three patients (72%) had complications, which are displayed in Table 1. The median duration of symptoms was 10 months [1–53]. Fifteen patients (47%) had anaemia, 28 (88%) had hypokalaemia and 18 (56%) had metabolic acidosis. Twenty-two patients (69%) had acute renal failure. The median serum creatinine level was 188 µmol/L [43–700]. The median serum albumin level was 28 g/L [13–41]. Twenty-three patients (72%) had vitamin or mineral deficiency.

Eleven of 18 patients tested were HLA DQ2 or DQ8 positive. Anti-transglutaminase, anti-endomysium, anti-gliadin and anti-enterocyte antibodies were negative (30/31, 21/21, 11/12 and 13/13 respectively). The patient with positive anti-transglutaminase antibodies (19 IU/mL; upper limit = 7) normalised her antibody levels on further dosages, including those achieved after gluten reintroduction. Anti-nuclear antibodies were positive (9/11) at a median level of 1/1280 [1/320–1/1600].

An upper GI endoscopic description was available for 29 patients (91%) and showed a normal duodenum in 15 cases (52%), an atrophic aspect with mosaic mucosa in 12 cases (41%), ulcerations in four cases (14%). Gastritis was found in two cases (7%). Endoscopic appearance of the jejunum or ileum was described for 17 patients (53%), either by capsule endoscopy or by ileocolonoscopy. Eight patients (47%) had normal small bowels on endoscopy, six patients (35%) had an atrophic aspect and two patients (12%) had jejunal and/or ileal ulcerations. Histological analysis of duodenal biopsies showed villous atrophy in all cases (32/32; 100%), mostly subtotal or total (26/30; 87%). Seventeen of 26 patients (65%) had counts of intra-epithelial lymphocytes of 30/100 epithelial cells or more. There was a lymphocytic infiltrate of the lamina propria (31/32; 97%), crypt hypertrophy (9/26; 35%); and, in two patients, collagen sprue (2/26; 8%). All intra-epithelial lymphocytes were CD3+ (18/18; 100%), CD8+ (14/14; 100%) and were polyclonal as indicated by the lack of detectable clonal T-cell receptor gamma rearrangement in duodenal biopsies (11/11). Lymphocytic colitis was found in four cases. Phenotypic studies of peripheral blood lymphocytes were performed in eight patients during olmesartan treatment and did not show any specific pattern, except for the presence of activated T cells in three of five patients tested (15% CD4+DR+, 45% CD4+CD25+, 52% CD8+DR+).

Table 1 | Complications observed in patients with olmesartan-associated enteropathy

Complications	Patients with villous atrophy, N = 32	Patients with normal villi, N = 4
Dehydration	14	3
Sepsis	5	–
Venous thrombosis	5	–
Cardiac arrhythmia	4	–
Pulmonary oedema	2	–
Pancreatitis	1	–
Rhabdomyolysis	1	–
Hyperosmolar coma	–	1
Ischaemic colitis	1	–
Steroid-associated fracture of the femur	1	–
Total number of patients	23	3

Outcome

No patient died. Thirty-one patients were hospitalised. The median cumulative hospital stay was 29 days [8–460]. Four patients required intensive care (12 days [5–22]). Seven patients required enteral nutrition (30 days [7–100]) and 10 required parenteral nutrition (29 days [10–291]). At the time of diagnosis, olmesartan was not known as a potential cause of enteropathy; therefore most patients were treated as if they had an autoimmune enteropathy. Nine of 14 patients responded to corticosteroids. Some patients received immunosuppressants, either alone or combined with corticosteroids. Four of five, one of two and six of seven patients achieved remission with thiopurines, tacrolimus and anti-TNF respectively. In total, 14 of 15 patients had remission with steroids and/or immunosuppressants. A gluten-free diet (GFD) was introduced in 21 patients and was insufficient in the 13 patients in whom it could be evaluated. Response to the GFD could not be evaluated in eight patients [two with only 3 and 7 days of the GFD and six in whom the GFD was introduced concomitantly with steroids (n = 1) or olmesartan withdrawal (n = 5)].

Twelve patients had 23 olmesartan interruptions followed by reintroductions. All of them were performed

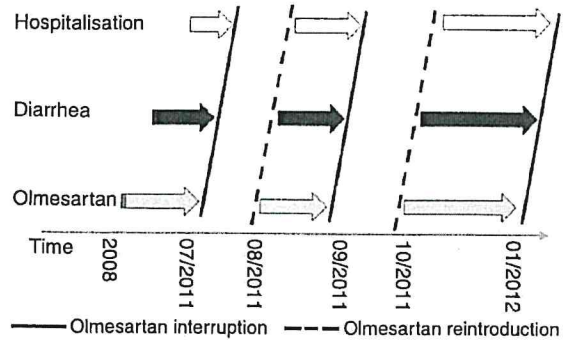

Figure 1 | The effect of interruption and reintroduction of olmesartan in a patient with olmesartan-associated enteropathy. Olmesartan (grey arrow) was stopped because of hypotension due to severe diarrhoea. Interruption of olmesartan led to improvement of diarrhoea (black arrow) and discharge from hospital (white arrow). Olmesartan was started again, which led to relapse of diarrhoea and hospitalisation.

before physicians were aware of the olmesartan-associated enteropathy. In most cases, interruptions were motivated by hypotension and reintroduction was motivated by patient improvement. We studied the 10 olmesartan interruptions and reintroductions performed before initiating treatment with steroids and immunosuppressants, to avoid the effect of these confounders. Olmesartan interruptions were followed by clinical remissions in 9 of 10 cases. Olmesartan reintroductions were followed by clinical relapses in nine of nine cases. An illustrative case is shown on Figure 1.

Exactly, 29/32 patients had been in clinical remission with a median follow-up of 8 months [0–40] since olmesartan interruption, including 26 with no immunosuppressants. Two patients were in remission with olmesartan and immunosuppressants (Infliximab and purinethol for one, azathioprine for the other) and one patient was not in clinical remission, 1 month after olmesartan withdrawal.

Four cases of olmesartan-associated sprue have occurred since the electronic alert in July 2013. None of these patients were prescribed systemic steroids or immunosuppressants and all completely recovered after olmesartan was stopped. In these four patients, the median time from the first symptoms to olmesartan cessation was 3 months [1–4] and the median duration of symptoms was 3 months [2–4]. Comparatively, in the rest of the cohort, the median time from the first symptoms to olmesartan cessation was 9 months [0–68] and the median duration of symptoms was 11 months [1–53]. Fifteen patients with villous atrophy had duodenal biopsies 9 months [2–39] after olmesartan cessation: the biopsy results came back normal for all of them.

Enteropathy with normal villi associated with olmesartan

Four patients (one man and three women, aged 55–74) had enteropathy and no villous atrophy. Three of them had a personal history of autoimmune or inflammatory disease (Table S1). One patient received 10 mg of olmesartan, the others received 40 mg. Three patients received other treatments concomitantly with olmesartan (Table S2).

Symptoms appeared 49 months [0–114] after olmesartan prescription and went on for 10 months [6–24]. All patients had diarrhoea, three had abdominal pain and one had vomiting. Body weight loss was 10% [0–23]. Three patients had hypokalaemia, one had metabolic acidosis, three had severe dehydration and acute renal failure (one patient required dialysis); one patient had hyperosmolar coma (Table 1). Two patients had low serum albumin level, respectively 27 and 29 g/L. None had anti-transglutaminase, anti-gliadin, anti-endomysium or anti-enterocyte antibodies. One patient was DQ2+. Endoscopic duodenal description was available in three patients; it showed an atrophic aspect in one case and duodenal ulcerations in two cases. On histological examination, two patients had elevated intra-epithelial lymphocyte counts (>30/100 epithelial cells) and three patients had lymphocytic infiltrate of the lamina propria. Three patients had microscopic colitis (two collagen colitis, and one lymphocytic colitis).

No patient died. Three patients were hospitalised (12 days [12–22]), and two required intensive care. No patient received artificial nutrition, steroids or immunosuppressants. No patient responded to the gluten-free diet. All patients recovered after olmesartan withdrawal. Two patients had olmesartan reintroduction; one relapsed and eventually achieved remission after the second olmesartan interruption. One patient relapsed 1 month after olmesartan withdrawal and remained steroid-dependent; he had collagen colitis.

Enteropathy associated with irbesartan

A 54-year-old woman has received irbesartan for hypertension since August 2011. From May 2012, she has had abdominal pain, 39% body weight loss, and acute renal failure. Duodenal biopsies showed total villous atrophy. Anti-transglutaminase, anti-endomysium, anti-enterocyte

antibodies and HLA DQ2/DQ8 were negative. Irbesartan was stopped in July 2013. Clinical remission was obtained, parenteral and enteral nutrition was stopped, and the patient was discharged from the hospital.

DISCUSSION

This study confirms the association between olmesartan and a sprue-like enteropathy, which is very similar with that described by Rubio-Tapia *et al.*[15] We also describe patients with severe clinical enteropathies without villous atrophy. Olmesartan is likely to be causal, as interruptions were followed by clinical remissions and reintroductions were followed by relapses. The association seems much more common with olmesartan than with other sartans.

Patients included in this study had a severe course. Some of them had life-threatening diarrhoea with acute renal failure, severe hypokalaemia and metabolic acidosis, leading to prolonged hospitalisation and, sometimes a visit to the ICU. They recovered after olmesartan withdrawal. The most recent cases had a shorter course than the early cases, thanks to the awareness of Gastroenterologists who immediately stopped olmesartan.

This study was performed throughout France, either in private or in public practice, tertiary referral hospitals as well as primary care. However, only gastroenterologists were contacted. This could have led to underestimate the frequency of olmesartan-associated enteropathy and biased the results towards the most severe forms.

This study supports the causality of the association between olmesartan and enteropathy. Firstly, our cases and those reported by Rubio Tapia *et al.* [15] were remarkably similar. Secondly, nondeliberate interruptions followed by reintroductions led to clinical remissions followed by clinical relapses respectively. Thirdly, as in the study by Rubio-Tapia *et al.*, duodenal mucosa returned to normal after olmesartan withdrawal. In addition, a recent epidemiological study performed in France has shown a significant association between hospitalisation for malabsorption and olmesartan prescription as compared with angiotensin-converting enzyme inhibitors and other sartans.[21] The lack of association between gastrointestinal events and olmesartan found in the ROADMAP trial [19] and in the paper by Padwal *et al.* [20] could be due to the confounding effect of diabetic neuropathy, which may provoke chronic diarrhoea. In addition, the incidence of olmesartan enteropathy is low and may require large populations of patients to be clearly demonstrated.

We report four patients with olmesartan-associated enteropathy and normal villi. The clinical picture was that of severe diarrhoea, similar with that of patients with villous atrophy, and these four patients also improved after olmesartan withdrawal. These cases add to the description of olmesartan-associated enteropathy. It may include patients with a wide range of histological duodenal abnormalities, from isolated intra-epithelial lymphocytosis and lamina propria lymphocytic infiltration to total villous atrophy. In addition, there is evidence of involvement of almost the entire gut in this condition.[15, 22] Biopsies of the duodenum but also of the stomach and the colon should be performed in patients with suspected olmesartan-associated enteropathy.

Eleven of 18 patients with villous atrophy tested (61%) were either DQ2+ or DQ8+, the coeliac disease predisposing phenotype. However, coeliac disease serology was negative and patients did not respond to a gluten-free diet, meaning that olmesartan does not trigger coeliac disease, as observed with interferon [23] and ipilimumab.[24] Rather, olmesartan-associated enteropathy appears as a separate immune-mediated entity. Firstly, a past history of autoimmunity or inflammatory disorders is frequent. Secondly, it may be associated with anti-nuclear antibodies and circulating activated T cells. Thirdly, all patients tested had polyclonal CD3+ CD8+ intra-epithelial lymphocytosis, which could mimic type 1 refractory coeliac sprue. Finally, it appears to respond to steroids or immunosuppressants and/or anti-TNF monoclonal antibodies. However, olmesartan-associated enteropathy differs from autoimmune enteropathy because it is associated with anti-nuclear antibodies and not with anti-enterocyte antibodies. A lupus-associated protein-losing enteropathy has been described.[25] But it had been reported long before olmesartan was marketed. The clinical and pathological picture is very different from that of olmesartan-associated enteropathy. It typically occurs in young women. The main symptom is generalised oedema due to profound hypoalbuminaemia; diarrhoea is observed in only half of the cases. Eventually, small bowel endoscopy and biopsies are normal in a lupus-associated protein-losing enteropathy.

In conclusion, this study shows that olmesartan causes severe and potentially life-threatening enteropathy with or without villous atrophy. It appears to be a new disease that differs from other immune-mediated enteropathies, such as coeliac disease, lupus-associated protein-losing enteropathies and autoimmune enteropathies. The pathophysiology of olmesartan-associated enteropathies requires further investigation that may shed new light on

coeliac disease and intestinal auto immunity. Patients who receive and physicians who prescribe olmesartan should be advised to stop the drug if diarrhoea appears.

AUTHORSHIP

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Author contributions: Marthey L, Cadiot G, Seksik P, Pouderoux P, Lacroute J, Skinazi F, Mesnard B, Chayvialle JA, Savoye G, Druez A, Parlier D, Abitbol V, Gompel M, Eoche M, Poncin E, Bobichon R, Colardelle P, Wils P, Salloum H, Peschard S, Zerbib F, Malamut G, Carbonnel F: Acquisition of data. Marthey L, Cadiot G, Méresse B, Cerf-Bensussan N, Carbonnel F: Analysis of data, drafting and critical revision of the manuscript. All authors approved the final version of the manuscript.

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Declaration of personal interests: Marthey L has served as a speaker for Amgen Cadiot G declares no conflict of interest Seksik P has served as a consultant for Abbvie, MSD, Servier, and Biocodex, Pouderoux P, Skinazi F, Mesnard B, Druez A, Parlier D, Peschard S, Méresse B, Cerf-Bensussan N, Malamut G, Salloum H, Wils P, Gompel M, Lacroute J, Chayvialle JA, Eoche M, Poncin E, Bobichon R and Collardelle P declare no conflict of interest Savoye G has served as a speaker for MSD, Abbvie, Ferring, Vifor, HAC Pharma and Pharmacosmos Abitbol V has served as a speaker for Abbvie, MSD, Ferring, Vifor Zerbib F has served as a consultant and board member for Given Imaging, Addex Pharma, Shire Movetis, Almirall, Reckitt Benckiser and Mederi Therapeutics; and as a speaker for Abbvie, Coloplast and Mayoli Spindler Carbonnel F has served as an advisory board member for Otsuka and Genentech.

Declaration of funding interests: None

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Patients with olmesartan-associated enteropathy presenting past history of autoimmune or inflammatory disease.

Table S2. drugs prescribed concomitantly with olmesartan in at least two patients in the olmesartan-associated enteropathy cohort.

Table S3. extra-intestinal manifestations in patients with olmesartan-associated enteropathy.

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EXHIBIT 12

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Images of the Month

Duodenal Villous Atrophy in a TTG-Negative Patient Taking Olmesartan: A Case Report and Review of the Literature

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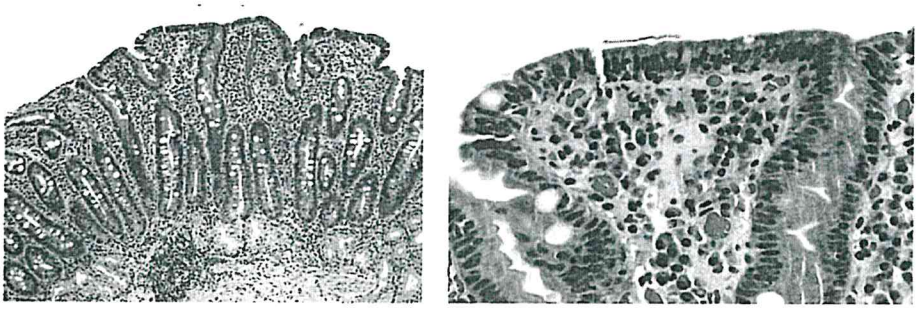
Olmesartan, an angiotensin II receptor antagonist used to treat hypertension, is associated with few adverse effects. Here, a case of severe sprue-like enteropathy and acute kidney injury is described in a 68-year-old male taking olmesartan for 3-4 years. He presented to hospital with a five-week history of diarrhea, vomiting, and a 20 lb weight loss. Anti-TTG was negative with a normal IgA. Biopsies of the distal duodenum and duodenal cap revealed marked blunting of the villi with near complete villous atrophy of the biopsies from the bulb. There was an increase in intraepithelial lymphocytes as well as neutrophils in the surface epithelium. The patient's diarrhea improved upon discontinuation of olmesartan and he returned to his previous weight. Repeat endoscopy four months later demonstrated complete resolution of inflammatory change with normal villous architecture. Long-term olmesartan use is associated with severe sprue-like enteropathy. The mechanism of intestinal injury is unknown. Duodenal biopsy results may mimic other enteropathies such as celiac disease. Physicians should consider medications as potential etiologies of enteropathy.

1. Case Presentation

A 68-year-old male presented to his family physician with a five-week history of nonbloody diarrhea, vomiting, and a 20 lb weight loss. Three days previously he had been seen by ophthalmology with new onset right eye pain, redness, and light sensitivity and diagnosed with severe right nongranulomatous anterior uveitis. He was treated with homatropine, dexamethasone, and prednisolone eye drops. He had no fevers, joint pain, skin changes, or recent travel. Past medical history included kidney stones, hypertension, and bioprosthetic aortic valve replacement three years earlier for severe aortic stenosis. He had been on olmesartan/hydrochlorothiazide 40/12.5 mg daily for 3-4 years. Other medications included ASA 81 mg twice weekly, vitamin C daily, multivitamin daily, cod liver oil daily, and acetaminophen as needed. Blood work ordered by his family physician included an elevated creatinine at 474 μmol/L. He was sent to the emergency department and admitted for an acute kidney injury presumably secondary to dehydration. Physical examination was unremarkable. He had normocytic anemia (hemoglobin 120 g/L), normal albumin (40 g/L), normal electrolytes, and nonanion gap metabolic acidosis. Creatinine improved to 77 μmol/L with intravenous fluids over 5 days. Stool was negative for culture, parasites, and *Clostridium difficile*. Anti-tissue transglutaminase (TTG) antibody was negative with normal immunoglobulin A levels. Biopsies of the distal duodenum and duodenal cap revealed marked villous blunting with near complete villous atrophy of the small intestinal mucosa in some areas (Figure 1). There was an increase in intraepithelial lymphocytes as well as neutrophils in the surface epithelium. The crypts had a prominent increase in apoptosis.

In hospital, his uveitis improved considerably and he was reassessed by ophthalmology. A diagnosis of idiopathic bilateral anterior and intermediate uveitis was confirmed after negative workup for syphilis, Lyme disease, sarcoid, and tuberculosis. The uveitis resolved at 16 weeks with a taper of prednisolone eye drops.

The patient's diarrhea resolved within 2 weeks of olmesartan discontinuation. His anemia improved to baseline and he returned to his previous weight within 3 months. Follow-up endoscopy 14 weeks later demonstrated complete resolution



(a) (b)

FIGURE 1: (a) Biopsy of the duodenum reveals villous blunting and expansion of the lamina propria inflammatory infiltrate (haematoxylin and eosin, original magnification ×100). (b) Higher power view of the surface epithelium from (a) shows increased intraepithelial lymphocytes (haematoxylin and eosin, original magnification ×400).

of the duodenal inflammatory changes and restoration of normal villous architecture (Figure 2).

2. Discussion

Olmesartan is an angiotensin receptor blocker (ARB) commonly prescribed in the management of hypertension. It is associated with few adverse effects, primarily dizziness, although diarrhea is noted in 1–10% of individuals [1]. Severe, sprue-like enteropathy associated with olmesartan was first described by Rubio-Tapia et al. in 2012 [2]. They reported 22 patients on olmesartan for a mean duration of 3.1 years presenting with diarrhea and weight loss. All patients were negative for anti-TTG antibody and were nonresponders to a gluten-free diet. Intestinal biopsies demonstrated villous atrophy in all patients, acute inflammation in 15 patients, and increased intraepithelial lymphocytes in 14 patients. Subepithelial collagen deposition was identified in seven patients. Pathologic changes in other organs included lymphocytic gastritis in five patients, collagenous gastritis in two patients, and microscopic colitis in five patients. Hospitalization for severe dehydration was required for 14 patients. Discontinuation of olmesartan resulted in clinical response in all patients and histopathologic resolution in 17 of 18 patients with follow-up intestinal biopsies performed after a range of 54–707 days. Several other case reports and series have reported similar findings, including a French national case series of 36 patients, with one case of irbesartan-associated enteropathy [3].

In an effort to determine if literature was emphasizing an exceedingly rare reaction to olmesartan or the most severe cases in a clinical spectrum of olmesartan-associated disease, a case-control study of 2,088 patients undergoing esophagogastroduodenoscopy and 12,428 patients undergoing colonoscopy was performed [4]. No association was identified between olmesartan use and diarrhea or histological diagnoses of celiac disease or microscopic colitis, suggesting that olmesartan-associated enteropathy is not part of a broader disease spectrum.

However, a recent retrospective cohort study of patients on ARBs with abdominal pain and no diarrhea reached a different conclusion. Lagana et al. found that 10 of 20 patients with abdominal pain on olmesartan had one or more sprue-like histological features [5]. There was a nonsignificant trend towards more sprue-like histologic features in patients taking olmesartan compared to patients taking other ARBs. This study suggests that there may be a wider spectrum of olmesartan-associated duodenal injury. The mechanism of intestinal injury and whether individuals exhibiting such histopathologic changes are at risk of developing a severe sprue-like enteropathy remains unknown. There are no previous documented cases of olmesartan-associated uveitis.

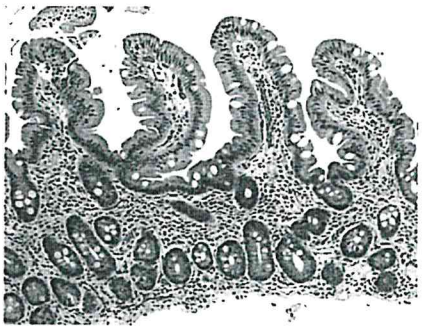


FIGURE 2: Follow-up biopsy 14 weeks after discontinuation of olmesartan shows striking normalization of the duodenal histology. There is normal villous architecture and no increase in intraepithelial lymphocytes in the biopsy (haematoxylin and eosin, original magnification ×100).

The case described here demonstrated full symptomatic and pathologic resolution after suspension of olmesartan within a four-month period. Given the life-threatening nature of the enteropathy, no rechallenge was instituted. In the assessment of enteropathy, physicians should be mindful of the broad differential diagnosis including medications, particularly olmesartan. Olmesartan-associated enteropathy may be of particular consideration in patients with seronegative duodenal villous atrophy or celiac disease refractory to gluten exclusion.

Competing Interests

The authors declare that they have no competing interests.

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Olmesartan induced enterocolitis

Sir,

Olmesartan is an angiotensin II receptor antagonist used for the management of hypertension. It has been available for prescription in Australia since February 2007.[1] Recently, Rubio-Tapia *et al.* reported a series of 22 cases of severe sprue-like enteropathy associated with olmesartan use.[2] We report a case with biopsy findings of sprue-like enteropathy with associated collagenous ileitis and colitis that showed complete resolution of histological and clinical symptoms following withdrawal of the medication.

The patient was a 78-year-old woman with a clinical history of hypertension, gastroesophageal reflux disease, hypercholesterolaemia and osteoarthritis, who had been prescribed olmesartan for 4 years. Other regular medications were lercanidipine, amitriptyline, atenolol and atorvastatin. There was no history of recent use of a non-steroidal anti-inflammatory medication. Over the past 4 months she had experienced severe watery diarrhoea which resulted in three hospital admissions, including an ICU admission for acute renal failure secondary to dehydration. Upper endoscopy and colonoscopy were performed to investigate the severe symptoms. Biopsies revealed mild villous blunting in the proximal small intestine with intraepithelial lymphocytosis and lamina propria inflammation (Fig. 1A). In the terminal ileum, and colonic biopsies, there was thickening of the subepithelial basement membrane, intraepithelial lymphocytosis and lamina propria chronic inflammation with eosinophil infiltration up to 50 per high power field (HPF) (×400; Olympus BX 41 microscope; Olympus, Japan) (Fig. 1B,C). Apoptosis was readily seen within the colonic crypts with up to 10 apoptotic bodies/HPF (×400; Olympus BX 41 microscope) (Fig. 1D). Gastric biopsies were not taken. An initial diagnosis of coeliac-like enteropathy, collagenous ileitis and collagenous colitis was made.

The differential diagnosis for this constellation of findings included coeliac disease, autoimmune enteropathy, chronic variable immunodeficiency (CVID)[3] and medication reaction. Of the patient's regular medications, olmesartan[2] and atorvastatin, a statin family medication,[4] have been reported with microscopic colitis; however, only olmesartan has been associated with a sprue-like enteropathy and hence it was considered the most likely drug culprit. Serum tissue transglutaminase antibodies were negative and the clinical setting did not support an autoimmune enteropathy or immunodeficiency syndrome. Withdrawal of olmesartan and atorvastatin with implementation of total parenteral nutrition and oral budesonide produced resolution of diarrhoea. On selectively recommencing only olmesartan and oral intake, the diarrhoea returned.

Her antihypertensive medication was subsequently changed to ramipril and the diarrhoea again resolved. A subsequent colonoscopy, performed 4 months after the initial biopsies, showed microscopically normal appearing small and large intestine with complete resolution of enteropathy-like changes and thickened collagen band (Fig. 2A,B).

Sprue-like enteropathy associated with olmesartan therapy was recently reported in a series of 22 cases.[2] In those with available detailed medical data, a mean interval between commencing olmesartan and developing diarrhoea was 3.1 years (range 0.5–7 years).[2] Baseline intestinal biopsies in all patients showed villous atrophy with seven cases displaying features of collagenous sprue. Three patients also exhibited collagenous colitis. All patients had negative serum

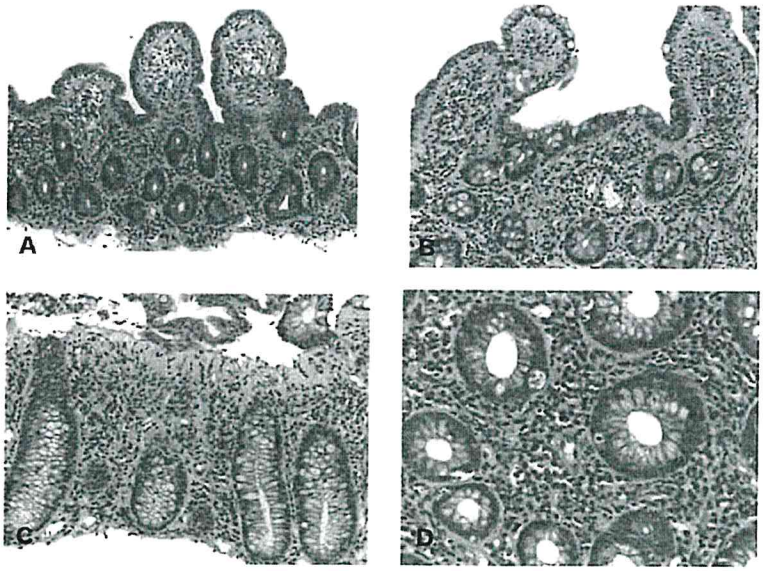

Fig. 1 (A) Proximal small intestinal biopsy displaying mild villous blunting and lamina propria inflammation. (B) Terminal ileal biopsy displaying mild thickening of the subepithelial collagen layer and lamina propria inflammation ('collagenous ileitis'). (C) Collagenous colitis. (D) Prominent crypt apoptosis in the colonic biopsies.

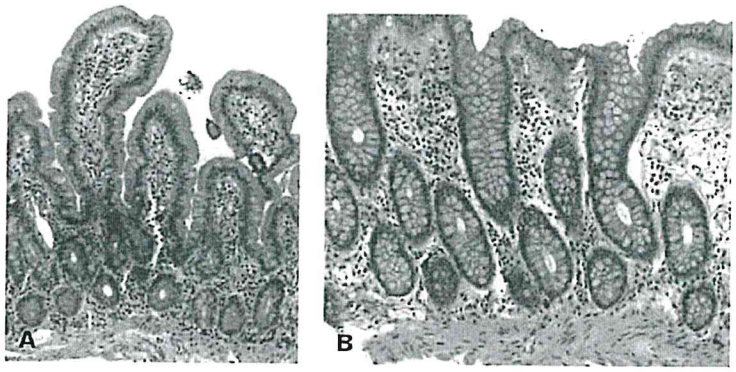

Fig. 2 Improvement in the appearance of histological features in (A) proximal small intestine and (B) colon following withdrawal of the drug.

tissue transglutaminase antibodies, and the symptoms and histological findings resolved completely after ceasing olmesartan. Twenty patients had been pre-treated with budesonide/corticosteroids prior to entering the study. To our knowledge, since this publication there have been 20 additional reported cases of suspected olmesartan associated enteropathy with either histological resolution, clinical resolution or both.[2,5–9] This includes 16 identified in a retrospective review of cases originally believed to represent coeliac disease, accounting for 84% of all mediation related duodenal villous atrophy.[7]

The mechanism associated with olmesartan related enteropathy is unclear. The typically long delay between commencing olmesartan and development of diarrhoea suggests cell mediated immune damage rather than a type 1 hypersensitivity reaction. Angiotensin II receptor antagonist inhibition of transforming growth factor beta (TGFβ) action, a molecule important for gut immune homeostasis,[2,3,5] and/or a cell mediated immune reaction that damages the small intestinal brush border[6] may be responsible.

There are marked similarities between our case and the series of olmesartan related enteropathy reported by Rubio-Tapia *et al.* While a medication reaction is always difficult to prove, the resolution of symptoms and histological findings in the absence of other medical conditions, suggest that this association is unlikely a result of chance. Furthermore, the conspicuous finding of apoptosis and the prominent eosinophilia in our case are features that can indicate a medication reaction.[10]

Olmesartan is a relatively new anti-hypertensive medication and it is possible that more cases of enteropathy will be seen in the future. Thus, it is important to consider olmesartan induced enteropathy in patients with histological sprue-like findings, with or without colonic inflammation, in the absence of other coeliac disease or other medical condition.

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High takeoff of the left main coronary artery at autopsy after sudden unexpected death in a male

Sir,

Coronary artery anomaly is a rare but important cause of sudden unexpected death, probably because of myocardial ischaemia.[1,2] One of these anomalies is high takeoff of the coronary artery, in which the ostium of the coronary artery is located above the sinotubular junction of the aortic valve.[3] Clinical and pathological reports of sudden death in patients with high takeoff of the coronary artery are extremely rare,[2,4] and the importance of this anomaly as a cause of myocardial ischaemia or sudden unexpected death is controversial. Here, we report the autopsy findings in a patient with sudden unexpected death in whom there was high takeoff of the left